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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,119	11/13/2001	Leu-Fen H. Lin	S225-M	4349

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,119	LIN ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,38,41 and 63-68* is/are pending in the application.

4a) Of the above claim(s) *37,38 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *37,38,41 and 63-68* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/13/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *892 references*.

DETAILED ACTION

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because 37 CFR 1.821 (a)(2)(c-d) states that *each sequence disclosed must appear separately in the* "Sequence listing" ***and in the text of the description*** and *claims whenever described.* For example, no amino acid sequence for the pre-pro GDNF sequence appears to exist, versus the nucleic acid sequence depicted as SEQ ID NO: 5. In other words, SEQ ID NOs: 5 & 8 are nucleotide sequences, versus amino acid sequences as currently disclosed. Accordingly, page 8 (1^{st} *pp*) and the description of Figures 19 & 22 on pages 13-14 must be amended to indicate the appropriate SEQ ID NOs being described, etc. See MPEP 2422 & 2431. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Note that failure to respond to both the requirements for sequence compliance and the restriction requirement below will be held as *nonresponsive*, and may result in *abandonment* of this application.

Election/Restrictions

2. Applicant's election with traverse of Group II (claims 63-68) in Paper No. 12/01/04 is acknowledged. The traversal is on the ground(s) that "the Director **may** require the application to be restricted to one of the inventions [emphasis added]", that "the Office Action provided broad and vague assertions that the groups defined were 'distinct' from each other and they have non-extensive searches and considerations" and therefore "[t]he standard applied in the present case then is clearly contrary to the controlling law described previously that demands that a

failure to restrict seriously burden (*sic*) the Examiner before a restriction is considered proper", that "[t]he only difference being that Group II includes a limitation wherein the GDNF is administered via a natural or cellular vectors", therefore, "the two groups are so closely situated that there would be no serious burden... with word based searches". This is not found persuasive because cell therapy is distinct from protein administration, which requires different starting materials, administration protocols, immuno-rejection considerations, blood brain barrier issues, etc., as illustrated by their art recognized differences in classification. Moreover, Applicant is incorrect in his assertion that "[t]he only difference being that Group II includes a limitation wherein the GDNF is administered via a natural or cellular vectors", for the reasons described above and for those reasons previously made of record. It is also noted that claims 63, 64 & 66-68 do not necessarily require any "administ[ration] via a natural or cellular vectors", but merely require cells that "secrete" GDNF, which technically is another group itself. For example, Class/subclass 424/93.1 versus 424/93.21; whereas the invention of Group I is 514/12. Nevertheless, cell implantation is not protein administration, which alternatively is a different search that creates a serious burden on the Examiner for both searching and examining these distinct inventions, for the reasons made of record, and because these two inventions are not obvious variants of the same method, but in contrast constitute different and distinct methods. The requirement is still deemed proper and is therefore made FINAL.

Claims 37-38 & 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12/01/04.

This application contains claims 37, 38 & 41 drawn to an invention nonelected with traverse in Paper No. 12/01/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 63-68 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

While the specification asserts a specific and substantial utility for the instant invention (e.g., pages 6-7 & 53 of the specification), "*preventing*... nerve damage" is not credible, because even normal aging results in death of neurons. Therefore, given the broadest reasonable interpretation consistent with that disclosed within the specification for the recitation, "*preventing*... nerve damage", which requires no naturally occurring loss of even a single neuron, is not credible, by definition; especially as it relates to treating neurodegenerative disease states that are characterized by neuronal cell death that further have no known treatment. See MPEP 2107.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-68 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5. Should Applicants amend the claims to remove the recitation of "preventing...", Claims 63-68 would then be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes the human GDNF polynucleotide of SEQ ID NO: 5 and the rat polynucleotide of SEQ ID NO: 3. In contrast, the specification fails to describe any polynucleotide molecules that encode polypeptides from any other species, and fails to describe any generic GDNF polynucleotide molecule. In other words, no adequate written description of a generic GDNF molecule exists within the instant specification, nor does an adequate written description exist within the specification for what critical encoded amino acids define any distinguishable and assayable GDNF function/activity. Therefore, one skilled in the art could not reasonably visualize what constitutes such generic DNA molecules encompassed by these claims that are required to practice the currently claimed method (i.e., as it relates to claims 63-67); thereby, not reasonably meeting the written description requirements under 35 U.S.C. 112, first paragraph. See MPEP 2163.

Second, pages 22 & 41 of the specification merely describe rat B49 glioblastoma cells that naturally secrete GDNF. In contrast, no normal non-tumorigenic cells amendable for practicing the currently claimed method are described within the instant specification that naturally secrete GDNF (i.e., as it relates to claims 63 & 66), such that one skilled in the art could reasonably visualize what cells "naturally... secrete glial derived neurotrophic factor", as currently and broadly claimed, without discovering such after-the-fact (provided any such cells even exist); thereby, also not reasonably meeting the written description requirements under 35 U.S.C. 112, first paragraph for claims 63-64 & 66-68.

6. Likewise, as indicated in the previous paragraph, if the utility rejection is obviated, claims 63-68 would then be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing uptake of dopamine in dopaminergic neurons using structurally characterized GDNF polypeptides secreted from cells implanted into the CNS within a biocompatible, semipermeable membrane, and transformed with a structurally characterized recombinant DNA molecule of SEQ ID NO: 5 that encodes human GDNF, does not reasonably provide enablement for any *in vivo* methods for "treating" unknown populations of neurons with structurally uncharacterized GDNF polypeptides using cell therapy subjected to immunorejection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification proposes a method of increasing survival of dopaminergic neurons or increasing dopamine uptake in Parkinson's patients using human GDNF. However, no

description of successfully using gene or cell therapy to generically "treat nerve damage" within the CNS is disclosed, nor known in the art. Nor would all neuronal populations be expected to contain receptors for human GDNF, and therefore, be targets for gene or cell therapy. Accordingly, page 2 of the specification states that "[a] given neurotrophic factor, in addition *to having the correct neuronal specificity*, must be available in sufficient quantity to be used as a pharmaceutical treatment [emphasis added]". Therefore, because only dopaminergic neurons are known in the art to be responsive to GDNF, and because only dopaminergic neurons are shown within the specification to be responsive to GDNF, it would require undue experimentation for the skilled artisan to discover what other putative neuronal populations, if any, may also be responsive to GDNF, as currently claimed, and what cells may putatively secrete GDNF, if any, for use in the currently claimed method.

Second, the state of the art is such that numerous problems exist concerning effective *in vivo* "treating nerve damage", because neuronal cell damage often results in cell death in the CNS, and because even "implanting" cells that secrete neurotrophic factors requires solutions to selectively target responsive cells, if known, with enough neurotrophic factor to elicit any response (i.e., through specific receptor binding; see page 2 of the specification), along with avoiding immuno-rejection of the implanted cells, as acknowledged on pages 41 & 42 of the specification. In other words, effective *in vivo* treatment, as it relates to treating any neuronal cell type with any protein, or implanted cell that expresses a protein, requires that one skilled in the art must know how, when or where the proposed invention is to be administered. In contrast, the instant specification has failed to disclose how these parameters are to be determined, what other specific neuronal populations are responsive to the encoded GDNF

polypeptides of the instant invention, how a similar disclosed method was practiced in the art with a different agent or cell, or to provide even a single *in vivo* working example of the claimed method. In other words, it cannot be successfully extrapolated from the limited *in vitro* tissue cultures disclosed using day 16 rat mesencephalic cells, or chick embryo ciliary ganglia and sympathetic chain ganglia (which all merely involve administering GDNF proteins, versus cell/gene therapy as claimed), whether the skilled artisan has successfully practiced Applicant's invention without requiring undue experimentation to first discover how to make and use Applicants' invention, as currently claimed; especially as it relates to determining the metes and bounds for "treating... [unknown properties of unknown neurons]" that alternatively encompass regeneration and resurrection of dead neurons (i.e., "nerve damage") that do not reasonably occur (e.g., see Jackowski, pg. 305, last *pp*).

Third, the unpredictability of the art related to gene/cell therapy, is as illustrated by the 1995 "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" which states that:

> "While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in *any gene therapy protocol*, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.
>
> Significant problems remain in all basis aspects of gene therapy. Major difficulties at the basic level include "*shortcomings in all current gene transfer vectors* and an *inadequate understanding of the biological interaction of these vectors with the host*" [emphasis added; page 1].

In other words, the unpredictability within the art in treating any generic neuron *in vivo* is compounded by the unpredictability within the art regarding successfully practicing any gene/ cell therapy protocol, as required to practice the instant invention, especially when attempting to affect unknown and undescribed neuronal populations and attempting to "treat" unknown

neuronal functions using the currently inadequately defined polynucleotides encoding uncharacterized GDNF polypeptides; thereby, reasonably requiring undue experimentation for the skilled artisan to known how to make and use the invention as currently claimed.

7. Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

SEQ ID NO: 5 is a nucleotide sequence, and not an amino acid sequence, as claimed; thereby, being indefinite.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
February 10, 2005

ROBERT C. HAYES, PH.D.
PATENT EXAMINER